20 November 2008

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

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Chem-Bio News– S&T Edition

1. EFFECT OF POLYETHYLENE GLYCOL MODIFICATION ON THE CIRCULATORY STABILITY AND IMMUNOGENICITY OF RECOMBINANT HUMAN BUTYRYLCHOLINESTERASE: *"These results suggest that PEG modification increased the circulatory stability of monomeric rHu BChE but failed to reduce or eliminate its immunogenicity."*

2. POTENTIATION OF AN ANTHRAX DNA VACCINE WITH ELECTROPORATION: *"These results suggest that EP may be a valuable platform technology for the delivery of DNA vaccines against anthrax and other biothreat agents."*

3. SIMULTANEOUS DETECTION OF SIX HUMAN DIARRHEAL PATHOGENS BY USING DNA MICROARRAY COMBINED WITH TYRAMIDE SIGNAL AMPLIFICATION: *"Consequently this assay is sensitive and a specific tool suitable for diagnostic detection and surveillance of multiple human pathogens."*

4. PROTECTION OF RED BLOOD CELL ACETYLCHOLINESTERASE BY ORAL HUPERZINE A AGAINST EX VIVO SOMAN EXPOSURE: NEXT GENERATION PROPHYLAXIS AND SEQUESTERING OF ACETYLCHOLINESTERASE OVER BUTYRYLCHOLINESTERASE: *"The increased doses of huperzine A used were well tolerated by these patients and in this ex vivo study sequestered more red blood cell AChE than has been previously demonstrated for pyridostigmine bromide (PB), indicating the potential improved prophylaxis against organophosphate (OP) poisoning."*

5. ANTI-INFLAMMATORY EFFECT FROM INDOMETHACIN NANOPARTICLES INHALED BY MALE MICE: *"The aerosol route required a therapeutic dose six orders of magnitude less than that for peroral administration."*

CB Daily Report

Chem-Bio News

EFFECT OF POLYETHYLENE GLYCOL MODIFICATION ON THE CIRCULATORY STABILITY AND IMMUNOGENICITY OF RECOMBINANT HUMAN BUTYRYLCHOLINESTERASE
Medical Devices & Surgical Technology Week
November 16, 2008

“Native Hu BChE is mostly tetrameric in form while the enzyme produced using molecular cloning technology is a mixture of tetramers, dimers, and monomers."

"Previous studies revealed that monomers and dimers of recombinant human (rHu) BChE cleared rapidly from the circulation of mice compared to tetrameric rHu BChE and native Hu BChE, which have mean residence times (MRTs) of 18h and 45h, respectively. It was also shown that polyethylene glycol-20K (PEG) modification of tetrameric rHu BChE prolonged its circulatory stability and bioavailability in vivo. The goal of this study was to determine if modification with PEG could prolong the circulatory stability and eliminate the immunogenicity of monomeric rHu BChE. Monomeric rHu BChE was expressed in human 293A cells using a cDNA lacking the 45 amino acid tetramerization domain from the carboxyl terminus and the adenovirus expression system. The catalytic and inhibitory properties of purified monomeric rHu BChE were similar to those for native Hu BChE and were not affected by PEG modification. As expected, monomeric rHu BChE rapidly cleared from the circulation of mice (MRT=3.2±0.3h) while monomeric PEG-rHu BChE demonstrated significant improvement in its bioavailability and circulatory stability in blood (MRT=31.4 ±5.4h). However, a second injection of monomeric PEG-rHu BChE, 28 days after the first, displayed a much shorter MRT=11.6±0.4h, and circulating anti-monomeric PEG-rHu BChE antibodies were detected in the blood of mice."

"These results suggest that PEG modification increased the circulatory stability of monomeric rHu BChE but failed to reduce or eliminate its immunogenicity."

The full article can be found at: (N. Chilukuri, et. al., “Effect of polyethylene glycol modification on the circulatory stability and immunogenicity of recombinant human butyrylcholinesterase”. Chemico-Biological Interactions, 2008;175(1-3):255-60). Link not available.

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POTENTIATION OF AN ANTHRAX DNA VACCINE WITH ELECTROPORATION
Vaccine Weekly
November 12, 2008

"DNA vaccines are a promising method of immunization against biothreats and emerging infections because they are relatively easy to design, manufacture, store and distribute. However, immunization with DNA vaccines using conventional delivery methods often fails to induce consistent, robust immune responses, especially in species larger than the mouse."

"Intramuscular (i.m.) delivery of a plasmid encoding anthrax toxin protective antigen (PA) using electroporation (EP), a potent DNA delivery method, rapidly induced anti-PA IgG and

toxin neutralizing antibodies within 2 weeks following a single immunization in multiple experimental species. The delivery procedure is particularly dose efficient and thus favorable for achieving target levels of response following vaccine administration in humans."

"These results suggest that EP may be a valuable platform technology for the delivery of DNA vaccines against anthrax and other biothreat agents."

The full article can be found at: (A. Luxembourg, et. al., “Potentiation of an anthrax DNA vaccine with electroporation”. Vaccine, 2008;26(40):5216-22). Link not available.

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SIMULTANEOUS DETECTION OF SIX HUMAN DIARRHEAL PATHOGENS BY USING DNA MICROARRAY COMBINED WITH TYRAMIDE SIGNAL AMPLIFICATION
Medical Devices & Surgical Technology Week
November 16, 2008

"Multiplex PCR and DNA microarray were combined with tyramide signal amplification (TSA) to develop a reliable method suitable for simultaneous detection of six species of human diarrheal pathogens (Yersinia enterocolitica, Shigella spp, Salmonella typhi, Brucella spp, Vibrio cholera and Escherichia coli O157:H7). Meanwhile, our method could distinguish V. cholera serotype O1 from O139, and O157:H7 from O157: non-H7."

"This assay conferred a specificity of 100% for target pathogens. The limit of detection was 103 degrees CFU/mL approximately. The results of 98.6% (357/362) clinical specimens and 100% (5/5) mocked double-blind samples were the same to that from conventional assay."

"Consequently this assay is sensitive and a specific tool suitable for diagnostic detection and surveillance of multiple human pathogens."

The full article can be found at: (D. Jin, et. al., “Simultaneous detection of six human diarrheal pathogens by using DNA microarray combined with tyramide signal amplification”. Journal of Microbiological Methods, 2008;75(2):365-8). Link not available.

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PROTECTION OF RED BLOOD CELL ACETYLCHOLINESTERASE BY ORAL HUPERZINE A AGAINST EX VIVO SOMAN EXPOSURE: NEXT GENERATION PROPHYLAXIS AND SEQUESTERING OF ACETYLCHOLINESTERASE OVER BUTYRYLCHOLINESTERASE
Biotech Week
November 12, 2008

"As part of a phase Ib clinical trial to determine the tolerability and safety of the highly specific acetylcholinesterase (AChE) inhibitor huperzine A, twelve (12) healthy elderly individuals received an escalating dose regimen of huperzine A (100, 200, 300, and 400

microg doses, twice daily for a week at each dose), with three (3) individuals as controls receiving a placebo. Using the WRAIR whole blood cholinesterase assay, red blood cell AChE and plasma butyrylcholinesterase (BChE) were measured in unprocessed whole blood samples from the volunteers following each dose, and then for up to 48h following the final and highest (400 microg) dose to monitor the profile of inhibition and recovery of AChE."

"Significant inhibition of AChE was observed, ranging from 30-40% after 100 microg to >50% at 400 microg, and peaking 1.5h after the last dose. Gradual recovery of AChE activity then occurs, but even 48 h after the last dose red blood cell AChE was about 10% below control (pre-dose) values. Huperzine A levels in plasma peaked 1.5h after the final 400 microg dose (5.47±2.15 ng/mL). Plasma BChE was unaffected by huperzine A treatment (as expected). Huperzine A-inhibited red blood cell (RBC) AChE activity was restored almost to the level that was initially inhibited by the drug."

"The increased doses of huperzine A used were well tolerated by these patients and in this ex vivo study sequestered more red blood cell AChE than has been previously demonstrated for pyridostigmine bromide (PB), indicating the potential improved prophylaxis against organophosphate (OP) poisoning."

The full article can be found at: (J.R. Haigh, et. al., “Protection of red blood cell acetylcholinesterase by oral huperzine A against ex vivo soman exposure: next generation prophylaxis and sequestering of acetylcholinesterase over butyrylcholinesterase”. Chemico-Biological Interactions, 2008;175(1-3):380-6).

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ANTI-INFLAMMATORY EFFECT FROM INDOMETHACIN NANOPARTICLES INHALED BY MALE MICE
Drug Week
November 21, 2008

“"There remains a need for an alternative means that is low cost, convenient, and capable of producing small-sized particles. On the other hand, one-third of the modern drugs are poorly water soluble. Many currently available injectable formulations of such drugs can cause side effects that originate from detergents and other agents used for their solubilization. The aerosol lung administration may by a good way for delivery of the water-insoluble drugs. We present here a new way for the generation of drug nanoparticles suitable for many water insoluble substances based on the evaporation-condensation route. In this paper the indomethacin nanoaerosol formation was studied and its anti-inflammatory effect to the outbred male mice was examined. The evaporation-condensation aerosol generator consisted of a horizontal cylindrical quartz tube with an outer heater. Argon flow was supplied to the inlet and the aerosol was formed at the outlet. The particle mean diameter and number concentration were varied in the ranges 3 to 200 nm and 10(3) to 10(7) cm(-3), respectively. The liquid chromatography and X-ray diffraction methods have shown the nanoparticles consist of the amorphous phase indomethacin. The aerosol lung administration experiments were carried out in the whole-body exposure chamber. Both the lung deposited dose and the particle deposition efficiency were determined as a function of the mean

particle diameter for mice being housed into the nose-only exposure chambers. The anti-inflammatory action and side pulmonary effects caused by the inhalation of indomethacin nanoparticles were investigated. It was found that the aerosol administration was much more effective than the peroral treatment."

"The aerosol route required a therapeutic dose six orders of magnitude less than that for peroral administration."

The full article can be found at: (A.A. Onischuk, et. Al., “Anti-inflammatory effect from indomethacin nanoparticles inhaled by male mice”. Journal of Aerosol Medicine and Pulmonary Drug Delivery, 2008;21(3):231-243). Link not available.

ANALYST NOTE: The Russians and their Soviet predecessors, have always been big proponents of aerosol immunization and therapy.

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END of CB Daily Report.

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